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Tolerating diabetes: an alternative therapeutic approach for diabetic neuropathy

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ABSTRACT

It is becoming apparent that a number of pathogenic mechanisms contribute to diabetic neuropathy, so that therapeutic interventions that target one particular mechanism may have limited success. A recently published preclinical study has adopted an alternative approach by using a novel small molecule to induce heat-shock protein 70. This confers upon neurons, and perhaps other cells of the nervous system, the ability to better tolerate the diverse stresses associated with diabetes rather than intervening in their production.

Key words: diabetes, diabetic neuropathy, heat-shock protein (HSP), heat-shock protein 70 (HSP70).

The increasing incidence of diabetes is placing ever-greater demands on health care systems. Not only does the disease lower life expectancy by 10–15 years, but quality-of-life is also impaired by progressive damage to the cardiovascular system, kidneys, eyes and nerves. These secondary complications of diabetes result from a combination of impaired insulin signalling, hyperglycaemia and dyslipidaemia, and ameliorating their physical and psychological consequences contributes significantly to the estimated $174 billion in yearly costs that have been attributed to diabetes in the US alone (http://www.cdc.gov/diabetes/pubs/factsheet07.htm; Centers for Disease Control 2007). Diabetic neuropathy is the most common of the complications of diabetes, with nerve damage developing in over 50% of all diabetic patients. Long-term studies have demonstrated that improving glycaemic control can slow onset and progression of neuropathy, but also suggest that hyperglycaemia is not the sole pathogenic factor involved, and that reversing established nerve damage is particularly difficult to achieve (Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2002). There is no FDA (Food and Drug Administration) approved drug for diabetic neuropathy and improved glycaemic control is the standard of care in most countries. Achieving tight glycaemic control by conventional means, such as insulin injections or pump delivery, diet control and glucose-modulating drugs, remains challenging for physician and patient alike. Recognizing that the means of achieving perfect glycaemic control for all diabetic patients is not yet at hand, many investigators have adopted a parallel approach that seeks to indentify the pathogenic cascades that flow downstream from insulinopaenia and hyperglycaemia in the hope of discovering alternative sites for therapeutic intervention. It may be fair to say that there has been much scientific progress in this regard over the last 40 years, but no clinical breakthrough.

The paper recently presented in *ASN NEURO* by Urban et al. (2010) reports an unusual approach to identifying a potential therapy for diabetic neuropathy. The authors have used the emerging appreciation of the roles of HSPs (heat-shock proteins) in cellular stress and survival pathways to identify an agent that does not rely on targeting a specific pathogenic mechanism, but rather manipulates the capacity of cells to tolerate otherwise toxic stresses. Specifically, they report the characteristics of KU-32, a small molecule based on novobiocin, which inhibits HSP90, thereby inducing neuroprotective HSP70. The authors go on to test the capacity of HSP70 induction to protect cells of the nervous system from exogenous stressors. It is particularly noteworthy that the study treads carefully through the minefield that is the modelling of diabetic neuropathy by using a diverse collection of assays that range from acute glucotoxicity directed at embryonic sensory neurons in culture, to phenotyping of sensory and motor nerve dysfunction in Type 1 diabetic mice.

Efficacy of KU-32 in a mouse model of diabetic neuropathy is demonstrated by intervention against established indices of nerve dysfunction. This contrasts with most preclinical studies, which tend to report the ability of a therapy to prevent onset of neuropathy – a design that equates to a

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Abbreviations: HSP, heat-shock protein; IENF, intra-epidermal nerve fibres; MNCV, motor nerve conduction velocity.

clinical trial with treatment beginning at diagnosis of diabetes. Such clinical trials are viable and any drug shown to be effective would have great commercial potential, as it would require all diabetic patients to take the drug from diagnosis of the disease for life. However, prevention studies can be prohibitively expensive, as they require large populations of patients to be followed over many years due to the unpredictable incidence and progression of diabetic neuropathy. By using an intervention paradigm, the authors have set a higher bar for success, as it is not clear that all indices of neuropathy may be amenable to reversal once established. However, preclinical success offers the potential of a more practical design for future clinical trials, in which smaller cohorts of patients with measurable neuropathy can be used to assess subsequent recovery.

Urban et al. (2010) use the intervention paradigm to show that KU-32 is effective against a number of indices of peripheral neuropathy. Behavioural tests of nocifensive responses to sensory stimuli are particularly amenable to these studies, as they allow iterative testing to identify onset of a disorder and subsequent responses to drug intervention. It is also tempting to extrapolate impaired nociception in these tests to the sensory loss reported by most patients with diabetic neuropathy. All such behavioural studies in rodents carry the caveat that depressed nocifensive responses can reflect disruption of sensory input, central processing or effector systems, although the frequent concern that impaired responses in diabetic animals are caused by the cachexia that accompanies Type 1 diabetes are offset in the present study by noting that KU-32 did not alter any systemic indicators of diabetes, such as hyperglycaemia or weight loss (Table 1 in Urban et al., 2010). Interestingly, both the presence of thermal hypoalgesia in untreated diabetic mice and the reversal of hypoalgesia by KU-32 occur in the absence of loss of IENF (intra-epidermal nerve fibres), which include the heat-sensitive C fibres. Loss of IENF is frequently reported in diabetic patients and rodents, and quantification of IENF in skin biopsies is being developed as a measure of small fibre neuropathy (Lauria et al., 2010). However, thermal hypoalgesia precedes detectable IENF loss in diabetic mice (Beiswenger et al., 2008) and the present data set further emphasizes that other mechanisms may also be involved. It takes 3–4 weeks of treatment with KU-32 treatment to reverse loss of sensation to tactile and thermal stimuli (Figure 5 in Urban et al., 2010), which is consistent with the time course of action of another HSP70 inducer in a model of physical nerve injury (Kalmar et al., 2003) and might argue against an acute neurochemical mechanism of action. The impact of KU-32 on other diabetes-induced changes to sensory neurons that could contribute to loss of sensory function, such as impaired synthesis, axonal transport and release of neuropeptides may warrant investigation.

KU-32 also shows efficacy against MNCV (motor nerve conduction velocity) slowing. The ability to prevent or reverse MNCV slowing in diabetic rodents has historically been the gold standard for demonstrating therapeutic potential of treatments for diabetic neuropathy, as diabetic patients show a similar slowing of large fibre conduction early in their disease that is predictive of future degenerative neuropathy. However, the literature now contains hundreds of diverse treatments that have ameliorated conduction slowing in diabetic rodents, without ever progressing to clinical use, and this plethora of false positives has somewhat tarnished the gold. In part, this may be because conduction slowing in clinical diabetic neuropathy involves pathogenic components that are not present in most rodent models of diabetes, such as segmental demyelination. Indeed, the lack of pathological damage to Schwann cells is a significant failing of most rodent models of diabetic neuropathy. The use of neuregulin-mediated demyelination in a neuron–Schwann cell co-culture system (Figure 3 in Urban et al., 2010) is a creative approach to circumnavigating the limitations of current animal models, and the efficacy of KU-32 in preventing demyelination adds another facet to its therapeutic potential. Although no single demonstration of efficacy in model systems can guarantee clinical success, the cumulative evidence offered in the paper by Urban et al. (2010) using diverse assays makes a relatively compelling case for the viability of KU-32 as a potential therapeutic.

The challenge for development of KU-32 is where to go next. Dose range and long-term toxicity issues clearly need to be addressed for a drug treatment approach that patients would be required to adopt for the rest of their lives. The use of HSP70-deficient mice to confirm involvement of this protein in the mechanism of action of KU-32 (Figure 6 in Urban et al., 2010) is elegant and the authors note that extension of mechanistic studies, particularly to identify the downstream consequences of HSP70 induction and the cell types in which it occurs after systemic administration of KU-32, will provide valuable information. The efficacy of KU-32 against diverse functional disorders encourages optimism for success against symptomatic neuropathy, which represents the target currently set by many regulatory agencies. However, diabetic neuropathy is a degenerative disease and, as mentioned above, most animal models show limited degenerative changes. Studies in diabetic animals that develop IENF loss may be of value, as this is a feature of both experimental and clinical diabetic neuropathy and few agents have yet been reported that restore IENF density in a reversal paradigm. The authors also speculate that KU-32 may have the potential to ameliorate aspects of painful diabetic neuropathy and indeed induction of HSP70 has previously been shown to ameliorate allodynia in a model of neuropathic pain induced by physical nerve injury (Kalmar et al., 2003). Studies in animal models of diabetes that show allodynia and hyperalgesia are clearly warranted.

The cost of clinical trials against degenerative neuropathy is a major obstacle to drug development for all but the largest companies. Success in alleviating pain may facilitate a faster track to clinical use, due to the shorter duration of clinical trials and because the template for achieving regulatory approval has already been established by drugs that suppress pain without preventing the underlying degenerative neuropathy. A therapy that treats both the pain and neurodegeneration of diabetic

neuropathy offers a viable route to regulatory approval and long-term benefit to patients. By manipulating cellular tolerance of stress, KU-32 may highlight a therapeutic approach more suited to addressing the diverse pathogenic mechanisms that contribute to diabetic neuropathy than attempts to intervene against any particular mechanism.

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